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A single-center study of pertuzumab-trastuzumab chemotherapy versus trastuzumab-chemotherapy in neoadjuvant treatment of breast cancer

Real-life data on neoadjuvant HER2 dual blockade

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Abstract

Aim: In recent years, neoadjuvant chemotherapy constitutes the basic building blocks of thetreatment scheme in the treatment of breast cancer. Randomized controlled studies in recent years have shown that neoadjuvant chemotherapy and dual anti-Her2(human epidermal growth factor receptor 2) combinations increase the pathological complete response and contribute to overall survival in Her2 positive breast cancer. The aim of this study is to compare the pathological complete response rates of patients receiving neoadjuvant chemotherapy-trastuzumab (CT) and patients receiving neoadjuvant chemotherapy-trastuzumab-pertuzumab (CTP) and present real-life data.

Material and Methods: 79 patients who received neoadjuvant CT and 155 patients who received CTP were included in the study. Pathological complete response rates of two independent groups were compared. Variables that predicted pathological complete response in both groups were examined.

Results: In real life, we found that the pathological complete response rates in patients receiving neoadjuvant CTP were much higher than the rates in patients receiving neoadjuvant CT, even higher than the rates in randomized controlled studies that led to the introduction of dual blockade into the literature.

Discussion: We think that neoadjuvant chemotherapy and dual anti-Her2 therapy are the optimal treatment for Her2 positive breast cancer.

Keywords

Neoadjuvant Therapy, Breast Cancer, Pertuzumab, Dual Anti-Her2 Treatment, Pathological Complete Response

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Introduction

In women, breast cancer is the most common type of cancer and the second leading cause of death from cancer [1]. Among breast cancers 20–25% of breast cancers overexpress HER2 (human epidermal growth factor receptor 2) and are associated with poor prognosis if untreated [2]. Signaling pathways that support cell proliferation, resistance to apoptotic signals, enhanced cell motility, and neoangiogenesis are constitutively activated as a result of HER2 gene amplification [3]. In comparison to chemotherapy alone, addition of trastuzumab, a HER2-directed humanized monoclonal antibody, dramatically increases response rate and overall survival in patients with metastatic HER2-positive breast cancer [4]. Trastuzumab inhibits ligand-independent signaling and prevents HER2 cleavage [5]. Specifically, between HER2 and HER3, ligand-dependent signaling is inhibited by pertuzumab, which is how it produces its effects. Trastuzumab and pertuzumab have complementary modes of action because they bind to separate locations [6].

In patients with localized or locally advanced Her2-positive breast cancer the pathological complete response rates (pCR) were increased by adding pertuzumab alongside trastuzumab as a neoadjuvant therapy [7]. In phase 2 neoSphere study, the pCR rate was increased by adding neoadjuvant docetaxel and trastuzumab alongside pertuzumab (29% vs. 46%). Another phase 2 trial, TRYPHANE, increased the effectiveness of trastuzumab-docetaxel by combining it with pertuzumab. In this study, the carboplatin arm's pCR was 51%, compared to 45 and 50% in the anthracycline arms [8]. At the same time, studies have shown that pCR is associated with overall survival [9].

Our study aims to compare the pathological complete response rates of neoadjuvant pertuzumab-trastuzumab-chemotherapy and trastuzumab-chemotherapy. To evaluate the correlation of real-world data with the literature.

Material and Methods

The patients who received neoadjuvant chemotherapy and trastuzumab in 2014-2018, and patients who received neoadjuvant pertuzumab, trastuzumab and chemotherapy in 2018-2022 were evaluated in this retrospective study T1-T4 and N0-N3, Her2 positive breast cancer patients over 18 years of age, were included in the study. Patients, those had metastatic disease at the time of diagnosis, and patients who could not complete neoadjuvant four cycles of pertuzumab-trastuzumab therapy were excluded from the study. In the trastuzumab group, patients who could not complete the neoadjuvant 12-cycles trastuzumab were excluded from the study.

The pertuzumab was given at a dose of 840 mg (cycle 1), followed by 420 mg every 3 weeks. Trastuzumab was given every 3 weeks at 8 mg/ kg (cycle 1), followed by 6 mg/kg in the other cycles. In the group receiving only trastuzumab, trastuzumab was given as 4mg/kg in the first week and 2mg/kg in the following weeks. Docetaxel was given at 75-100 mg/m^2 every 3 weeks. Paclitaxel was given at 80 mg/m^2 on days 1, 8, and 15 or 175 mg/m2 every 3 weeks. Anthracycline protocol was administered to patients as Adriamycin cyclophosphamide (AC) or fluorouracil, epirubicin, and cyclophosphamide (FEC). The AC protocol contained 60 mg/m2 Adriamycin + 600 mg/m^2 cyclophosphamide every 3 weeks. It contained fluorouracil at 600 mg/m^2, epirubicin at 90 mg/m^2 and cyclophosphamide at 600 mg/m^2 intravenously every 3 weeks in the FEC protocol. Patients received trastuzumab or trastuzumab emtansine (TDM-1) for 1 year after surgery.

Data of Her2 positive breast cancer patients receiving neoadjuvant chemotherapy were obtained from hospital records. The demographic characteristics of the patients, the treatment regimens they received in the neoadjuvant period, their surgical information, pathology reports, last examination dates, and if they died, date of death were recorded.

In this study, the primary endpoint was determined as pCR. The absence of invasive tumors in primary breast tissue and axilla was considered as a pathological complete response. The presence of only residual ductal carcinoma insutu(DCIS) was also evaluated as a pCR.

The patients were divided into two groups as those who received taxane pertuzumab trastuzumab and those who received taxane trastuzumab. Demographic features, clinicopathological features and pCR of these two groups were compared. Then, both groups were divided into two subgroups as those with and without pCR, and their clinicopathological features were compared.

Statistical Analysis

In the descriptive statistics of the study, continuous variables were used as mean (standard deviation), median (range); categorical variables were presented as frequency (percentage). Chi-square or Fisher's Exact test was used to compare the categorical variables of two independent groups. Independent sample t-test for comparison of parametric data; The mann-whitney-u test was used to compare non-parametric data. A logistic regression model was created with variables with a p-value of <0.100, and independent factors predicting pathological complete response were identified.

Ethical Approval

This study was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Oncology Educatin and Research Hospital (Date: 26-07-2023, No: 2023-07/297)

Results

A total of 79 patients in the trastuzumab group and 155 patients in the pertuzumab-trastuzumab group were included in the study. The median age was 49 years in both groups. While the T stage was distributed as T2-T4 in the group receiving trastuzumab, the T2 stage was predominant in the group receiving pertuzumab-trastuzumab (p<0.001, Table 1). While axilla positivity was observed in all patients receiving trastuzumab at the time of diagnosis, 11 (7.1%) of the patients receiving pertuzumab-trastuzumab were axilla negative at the time of diagnosis (p:0.015). Ki-67 median was 40 in both groups. Patients receiving neoadjuvant anthracyclines predominated in both groups, and a minority of patients in both groups received dose-dense AC (Table-1).

The median age in the all-patient group was 49 years. When the factors predicting pathological complete response were evaluated in the all-patient group, the estrogen receptor status was observed to be significant (p:0.046), while the progesterone receptor status (p:0,107) and T-stage (0,087) were at the

border. Estrogen receptor status was found to be significant when the logistic regression model was applied for all patients group.

The median age of patients with pCR and non-pCR was 53 vs 47 years in the trastuzumab group (p:0.022). In pertuzumab-trastuzumab group, premenopausal patients was found to be significantly higher in patients with pCR than in patients with non-pCR (53.7% vs. 36.4%, p:0.041). In the pertuzumab-trastuzumab group, progesterone receptor positivity was lower in patients with pCR than in patients with non-pCR (p:0.039). In pertuzumab-trastuzumab group estrogen receptor status, progesterone receptor status, and menopausal status were evaluated with a logistic regression model. Progesterone receptor (%95 CI 0,154-1,291 p:0.039) and menopause status (%95 CI 0,210-0,866 p:0.041) were the independent predictive factors for pCR (Tabie-2).

Table 1. Comparison of demographic and clinicopathologic features of the patients who received or not received pertuzumab as neoadjuvant therapy

	Trastuzumab	Pertuzumab	P -value
Age	49±11.1	49±12.4	0.811
Smoker			
No - ex-smoker	71 (89.9)	120 (77.4)	0.02
Yes	8 (10.1)	35 (22.6)	
Menopause			
Premenopausal	35 (44.3)	75 (48.4)	0.554
Post-perimenopausal	44 (55.7)	80 (51.6)	
Familial breast cancer			
Yes	8 (10.1)	30 (19.4)	0.070
No	71 (89.9)	125 (80.6)	
Clinical T stage			
T1	0	18 (11.6)	<0.001
T2	47 (59.5)	126 (81.3)	
T3-T4	32 (40.5)	11 (7.6)	
Clinical nodal status			
No	0	11 (7.1)	0.015
Yes	79 (100)	144 (92.9)	
Clinical Stage			
1b-2a	0	28 (18.1)	<0.001
2b-3	79 (100)	127 (81.9)	
ER status			
Positive	38 (48.1)	94 (60.6)	0.067
Negative	41 (51.9)	61 (39.4)	
PR status			
Positive	38 (48.1)	96 (61.9)	0.043
Negative	41(51.9)	59 (38.1)	
Her2 score			
3+	73 (93.6)	146 (94.2)	0.855
2+	5 (6.4)	9 (5.8)	
Ki 67, median, IQR	40 (30-50)	40 (30-60)	0.537
Grade			
Grade 1-2	13 (22.8)	42 (27.1)	0.334
Grade 3	44 (77.2)	100 (64.5)	
Neoadjuvant anthracycline			
Yes	76 (96.2)	146 (94.2)	0.510
No	3 (3.8)	9 (5.8)	
Dose-dense anthracycline			
Yes	3 (3.8)	11 (7.1)	0.314
No	76 (96.2)	144 (92.9)	

ER: Estrogen receptor, PR: Progesterone receptor

When the pathological complete response rates of the patients receiving trastuzumab and the patients receiving pertuzumab-trastuzumab were compared, pathological complete response was observed in 95 (61.2%) patients in the pertuzumab-trastuzumab group, while it was observed in 33 (41.7%) patients in the trastuzumab group. This difference was statistically significant (p:0.002).

Discussion

In our study, pathological complete response rates were found to be significantly higher in the group receiving dual blockade than in the group receiving only trastuzumab. In the neoSphere study, the pCR was found to be 45% in the group receiving pertuzumab-trastuzumab-dosataxel, while in our study, the pCR was found to be 61% in this group. In our study, it was thought that the pCR rates were higher because the patients also received anthracycline and cyclophosphamide in the neoadjuvant period [10].

In our study, the difference between the pathological complete response rates of patients receiving trastuzumab and those receiving pertuzumab-trastuzumab was significant. Since the study was retrospective, the patients were not distributed at similar stages in both groups. The frequency of T4 and N3 disease was higher in the group receiving trastuzumab. This difference was not statistically significant, but it was thought that starting neoadjuvant therapy at a later stage might reduce the pathological complete response and make the difference between the two groups more significant. The fact that the patients were more advanced in the trastuzumab group reflects the shift in our treatment trend to neoadjuvant therapy after the dual blockade. Likewise, the tendency of surgeons in recent years is to refer patients to neoadjuvant treatment at an earlier stage.

In the pertuzumab group, 53(%55.7) of the patients with pathological complete response were progesterone receptor positive, while 42(%44.3) patients were negative. In the group non-pCR, 40 (72.7%) patients were progesterone receptor positive and 15 (27.3%) patients were progesterone receptor negative. Pathological complete response was found to be lower in progesterone receptor-positive patients, this result was consistent with the literature [11]. It is known that the frequency of residuals after neoadjuvant therapy in triple-positive breast cancer is higher than in the Her2 positive-hormone receptor negative group [12]. In a study published in 2016, pathological complete response rates were compared according to tumor subtypes. The rate of pCR in Her2 and ER and PR positive patients was found to be lower than in Her2 positive patients and ER and PR negative patients [11]. It is associated with a lower treatment response of the hormone receptor-positive component.In the all-patient group, pathological complete response was found to be statistically lower in estrogen receptor-positive patients. Pathological complete response was significantly higher in premenopausal patients in the pertuzumab group(p:0.039)In the study conducted by Silva et al., pCR was found to be high in premenopausal patients, as in our study [13]. In addition, there

Table 2. A comparison of the patients with pCR and non-pCR according to neoadjuvant therapy

	Trastuzumab		p-value	Pertuzumab		p-value	All patients		p-value
	Non-pCR	pCR		Non-pCR	pCR		Non-pCR	pCR	
Age	47 ±11.5	53 ±9.9	0.022	51±11	47±12	0.098	49±11	49±12	0.862
Smoker									
No- ex-smoker	41 (89.1)	30 (90.9)	0.796	43 (78.2)	72 (75.8)	0.739	84 (84)	102 (79)	0.610
Yes	5 (10.9)	3 (9.1)		12 (21.8)	23 (24.2)		17 (16)	26 (21)	
Menopause									
Premenopausal	24 (52.2)	11 (33.3)	0.096	20 (36.4)	51 (53.7)	0.041	44 (43.5)	62 (48)	0.506
Peri-postmenopausal	22 (47.8)	22 (66.7)		35 (63.6)	44 (46.3)		57 (56.6)	66 (52)	
Familial breast cancer									
No	41 (89.1)	30 (90.9)	1	46 (83.6)	78 (82.1)	0.811	87 (86)	108 (84)	0.852
Yes	5 (10.9)	3 (9.1)		9 (16.4)	17 (17.9)		14 (14)	20 (16)	
Clinical T stage									
T1				5 (9.1)	11 (11.6)		5 (4.9)	11 (8.5)	
T2	26 (56.5)	21 (63.6)	0.525	45 (81.8)	78 (82.1.9	0.753	71 (70.3)	99 (77)	0,087
T3-T4	20 (43.5)	12 (36.4)		5 (9.1)	6.8 (6.3)		25 (24.8)	18 (14)	
Clinical nodal status									
Node positive	0	0		3 (5.5)	8 (8.4)	0.747	38 (2.9)	8 (6.2)	0.354
Node negative	46 (100)	33 (100)		52 (94.5)	87 (91.6)		98 (97.1)	120 (93.8)	
Clinical stage group									
1b-2a	0	0		8 (14.5)	18 (18.9)	0.493	8 (7.9)	18 (14)	0.208
2b-3	46 (100)	33 (100)		47 (85.5)	77 (81.1)		93 (92.1)	110 (86)	
ER status									
Positive	26 (56.5)	12 (36.4)	0.077	38 (69.1)	52 (54.7)	0.084	64 (63.3)	64 (50)	0.046
Negative	20 (43.5)	21 (63.6)		17 (30.9)	43 (45.3)		37 (36.7)	64 (50)	
PR status									
Positive	24 (52.2)	14 (42.4)	0.392	40 (72.7)	53 (55.7)	0.039	64 (63.3)	67 (52.3)	0.107
Negative	22 (47.8)	19 (57.6)		15 (27.3)	42 (44.3)		37 (36.7)	61 (47.8)	
Her2 score									
3+	41 (91.1)	32 (97)	0.389	52 (94.5)	90 (94.7)	1	93 (92)	122 (95.4)	0.568
2+	4 (8.9)	1 (3.9)		3 (5.5)	5 (5.3)		7 (8)	6 (4.6)	
Ki67,median	40 (8-90)	40 (8-80)	0.776	40 (10-80)	50 (3-95)	0.193	42 (8-90)	45 (3-95)	0.288
Grade									
Grade 1-2	6 (19.4)	7 (26.9)	0.498	16 (32.7)	24 (27.3)	0.507	22 (27.5)	31 (27)	0.545
Grade 3	25 (80.6)	19 (73.1)		33 (67.3)	64 (72.7)		58 (72.5)	83 (73)	
Neoadjuvant anthracycline									
Yes	44 (95.7)	32 (97)	1	51 (92.7)	90 (94.7)	0.725	95 (94)	122 (95)	0.769
No	2 (4.3)	1 (3)		4 (7.3)	5 (5.3)		6 (6)	6 (5)	
Dose-dense anthracycline									
Yes	2 (4.3)	1 (3.0)	1	2 (3.6)	8 (8.4)	0,326	4 (4)	9 (7)	0.396
No	44 (95.7)	32 (97.0)		53 (96.4)	87 (91.6)		97 (96)	119 (93)	

ER: Estrogen receptor, PR: Progesterone receptor

are also studies in the literature that support the opposite. In a study conducted in France in 2021, it was determined that the pathological complete response was seen at a lower rate in young and premeopausal Her2 positive patients, and this situation was associated with low DFS [14]. Similarly, in another study published in 2013, a lower rate of pathological complete response was found in premenopausal Her2 positive patients [15]. But it is also known that the tumor is more aggressive in young premenopausal patients [16]. The higher detection of pathological complete response in premenopausal patients in our study may be associated with a better response of aggressive tumors to neoadjuvant chemotherapy. This result suggested that aggressive tumors may benefit more from the neoadjuvant dual blockade.

Limitation

As for the limitations of our study; since it was retrospective, the clinicopathological features of the patients were not similarly distributed in the trastuzumab and pertuzumab-trastuzumab groups. Survival analyses could not be performed because the median follow-up time was short.

Conclusion

In conclusion, it is the standard combination of dual anti-Her2 and chemotherapy in neoadjuvant treatment in Her2 positive breast cancer. It has been shown in prospective studies and

real-life data that it increases the pathological complete response

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest
The authors declare that there is no conflict of interest.

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